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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/831,455	05/08/2001	Y Tom Tang	PF-0634 USN	4335

27904 7590 09/23/2003

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EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No.	Applicant(s)	
	09/831,455	TANG ET AL.	
	Examin r	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-45* is/are pending in the application.

4a) Of the above claim(s) *21,22,32-40 and 42-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-31 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received..

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *20* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

[1] Claims 21-45 are pending in the application.

[2] Applicant's amendment to the specification, cancellation of claims 1-20, and addition of claims 21-45 in Paper No. 19, filed July 03, 2003, is acknowledged.

Lack of Unity

[3] Applicant's election with traverse of Group XX, original claims 3-13, drawn to a polynucleotide encoding SEQ ID NO:6 including SEQ ID NO:22, in Paper No. 19 is acknowledged. Applicant traverses the lack of unity requirement (beginning at page 8 of Paper No. 19) by stating that the unity of invention standard must be applied in national stage applications. Applicant cites sections of MPEP § 1800 in support of their statements. In response to applicant's statements, it is noted that the unity of invention standard *was* applied to original claims 1-20 in evaluating the claims for unity of invention and restriction practice according to 35 U.S.C. 121 and 372. MPEP § 1893.03(d) states, "If the examiner finds that a national stage application lacks unity of invention under § 1.475, the examiner may in an Office action require the applicant in the response to that action to elect the invention to which the claims shall be restricted". Also, according to PCT Rule 13.2, unity of invention exists only when the shared same or corresponding technical feature is a contribution over the prior art. As stated in the Office action of Paper No. 18, the inventions of original claims 1-20 do not relate to a single general inventive concept because the shared technical features of the claimed polypeptide and polynucleotide lack novelty or inventive step and therefore, do not make these technical features a contribution over the prior art. See the Office action of Paper No. 18 for reasons why the inventions of original claims 1-20 lack unity of invention. In accordance with MPEP § 1893.03(d), the examiner properly applied the unity of invention standard to original claims 1-20 in the instant application.

Beginning at the top of page 9 of Paper No. 19, applicant cites Example 17, Part 2 of Annex B to the Administrative Instructions Under the PCT, which states:

Example 17
Claim 1: Protein X.
Claim 2: DNA sequence encoding protein X.
Expression of the DNA sequence in a host results in the production of a protein which is determined by the DNA sequence. The protein and the DNA sequence exhibit corresponding special technical features. Unity between claims 1 and 2 is accepted.

Applicant argues the examiner should withdraw the lack of unity requirement with respect to claims of Group V, drawn to the special technical feature of a polypeptide, and co-examine the claims of Group V with the elected claims of Group XX. Applicant argues unity of invention exists for claims drawn to the polypeptide of SEQ ID NO:6 and claims drawn to the elected corresponding encoding polynucleotide of SEQ ID NO:22 based on the rules concerning unity of invention under the PCT and Example 17 as stated above. Applicant's argument is not found persuasive. According to PCT Rule 13.2, unity of invention exists only when there is a shared same or corresponding special technical feature among the claimed inventions. The polynucleotide of claim 31, which is drawn to an isolated polynucleotide comprising at least 30 contiguous nucleotides of SEQ ID NO:22, encompasses polynucleotides that, when expressed, results in the production of proteins that *do not* correspond to the polypeptide of Group V. Therefore, the polynucleotide of Group XX, particularly the polynucleotide of claim 31, does not share a corresponding special technical feature with the polypeptide of Group V, and thus the inventions do not have unity of invention. Furthermore, according to PCT Rule 13.2, unity of invention exists only when the shared same or corresponding technical feature is a contribution over the prior art. The inventions of Groups V and XX do not have unity of invention because the technical feature of Groups V and XX do not contribute over the prior art. The technical feature of Group V is a polypeptide, which is shown by Sigma Chemical Company 1993 Catalog to lack novelty or inventive step because Sigma Chemical Company 1993 Catalog teaches a Gly-Gln bioactive peptide (page 1032), corresponding to amino acids 284 and 285 of SEQ ID NO:6 that is a biologically active fragment of SEQ ID NO:6 and does not make it a contribution over the prior art. Also, the technical feature of Group XX is a polynuncleotide, which is shown by Database GenBank Accession Number AA622495 (version AA622495, gi:2526371) to lack novelty or inventive step because Database GenBank Accession Number AA622495 teaches a polynucleotide encoding a

biologically active fragment of SEQ ID NO:6 comprising at least 30 contiguous nucleotides of SEQ ID NO:22 (see attached sequence alignment) and does not make it a contribution over the prior art.

Beginning at the middle of page 9 of Paper No. 19, applicant cites sections of MPEP § 1800 and argues newly added claims 22-27, 35, 36, and 43-45 should be co-examined because unity of invention exists with respect to dependent claims in the same claim category as the independent claim from which they depend. Applicant argues there is unity of invention among claims 21, 23, and 30 and thus, claims dependent therefrom have unity of invention. Applicant's argument is not found persuasive. As stated above, there is no unity of invention between the polypeptide of Group V and the polynucleotide of Group XX. Therefore, claims dependent from claims 21, 23, and 30, e.g., claims 43-45, drawn to an antibody that binds the polypeptide of Group V, do not have unity of invention with the claims of Groups V and XX because the polynucleotide of Group XX shares no corresponding technical feature with the polypeptide of Group V and neither of the special technical features of the inventions of Groups V and XX makes a contribution over the prior art. Furthermore, applicant's argument that claims 22-27, 35, 36, and 43-45 have unity of invention with the claim from which they depend, i.e., the polypeptide of claim 21, is misplaced. As is further explained in MPEP § 1850, if an independent claim does not avoid the prior art, then the question whether there is still an inventive link between all the claims dependent on that claim needs to be carefully considered. If there is no link remaining, an objection of lack of unity may be raised. As has been previously explained, the polynucleotide of Group XX and the polypeptide of Group V do not constitute a special technical feature and thus there is no inventive link between the polynucleotide of Group XX, the polypeptide of Group V and the antibody of claims 43-45. It should be noted that claims of Group XX which depend from the claims of Group V are not dependent claims that have unity of invention within the meaning of MPEP § 1850(A) as the polynucleotide claims of Group XX which depend from the polypeptide claims of Group V do not have all the features of the polypeptide, i.e., polypeptides and polynucleotides are *chemically distinct* compounds.

Beginning at the top of page 10 of Paper No. 19, applicant argues unity of invention exists among all of the pending claims. Applicant argues the claimed polypeptides and encoding polynucleotides

are corresponding technical features, which are common to all pending claims, which serve to technically interrelate all pending claims, and which define the contribution over the prior art. Applicant argues the pending claims are linked to form a single general inventive concept, and applicant is therefore entitled to prosecute all pending claims in a single application. Applicant's argument is not found persuasive. As stated above, the polynucleotide of Group XX does not share a corresponding special technical feature with the polypeptide of Group V and neither of the shared technical features of Groups V and XX make a contribution over the prior art. Furthermore, 37 CFR § 1.475(d) does not provide for the inclusion of multiple methods of use within the main invention. As claims 28 and 29 are the first claimed method of using the polynucleotide of Group XX, these claims will be included and co-examined with the claims of Group XX. However, the *additional* methods of use of the polynucleotide of Group XX and methods of using the polypeptide of Group V do not have unity of invention in accordance with PCT Rule 13.2 and 37 CFR § 1.475(d). Therefore, the polynucleotide of Group XX, the polypeptide of Group V, the antibody of claims 43-45, *additional* methods of using the polynucleotide of Group XX, and methods of using the polypeptide of Group V do not have unity of invention. It is noted that in the original claim groupings of Paper No. 18 the examiner included claim 7, drawn to a method for detecting a polynucleotide, as the first claimed method of using the polynucleotide of Group XX. However, due to applicant's re-ordering of claims in the amendment of Paper No. 19, claims 28 and 29, drawn to a method of producing a polypeptide using a host cell comprising a recombinant polynucleotide, is now the first claimed method of using the polynucleotide of Group XX and will be co-examined in accordance with 37 CFR § 1.475(d).

Beginning at the top of page 11 of Paper No. 19, applicant argues the sequences of the claimed polypeptides and corresponding polynucleotides are common to all pending claims. Applicant argues the sequences of the claimed polypeptides and corresponding polynucleotides serve to technically interrelate all of applicant's claims. Applicant argues the composition of matter claims are drawn either to the claimed polypeptides or polynucleotides themselves, to compositions of matter that comprise the polypeptides or polynucleotides as one element, or to compositions of matter wherein the sequences of the claimed polypeptides functionally limit the claimed subject matter. Applicant argues that in the

methods of claims 28, 29, 32-34, and 37-40, the claimed polypeptides or polynucleotides serve as either the product of the claimed method (claims 28-29) and/or as a reagent for performing the method (claims 32-34 and 38-40). Applicant's argument is not found persuasive. The examiner acknowledges that the polypeptide of SEQ ID NO:6 and the polynucleotide of SEQ ID NO:22 share a corresponding technical feature, i.e., the polynucleotide of SEQ ID NO:22 encodes the polypeptide of SEQ ID NO:6. However, the polynucleotide of elected Group XX is *not* limited to the polynucleotide of SEQ ID NO:22. As stated above, the polynucleotide of Group XX (including compositions thereof), the polypeptide of Group V (including compositions and methods of use thereof), the antibody of claims 43-45 (including compositions thereof), and the *additional* methods of use of the polynucleotide of Group XX do not share a corresponding technical feature and do not contribute over the prior art and/or are *additional* methods of use of an invention that already includes a method of use and do not have unity of invention in accordance with PCT Rule 13.2 and 37 CFR § 1.475(d).

Beginning at the top of page 12 of Paper No. 19, applicant argues there is minimal additional burden to examine claims 39-42. Applicant argues the search for the subject matter of these claims should substantially overlap with the examination of the polynucleotide of Group XX. To the extent applicant's argument applies to the microarray of claim 41, applicant's argument is found persuasive. It is noted that the polynucleotide of Group XX and the microarray of claim 41 share the same special technical feature, i.e., the polynucleotide of Group XX. Therefore, claim 41 will be co-examined with the claims of Group XX. To the extent applicant's argument applies to claims 39, 40, and 42, applicant's argument is not found persuasive. Regarding the methods of claims 39, 40, and 42, it is false to assume that a disclosure describing the sequence of a polynucleotide or microarray comprising said polynucleotide would also disclose methods of using the same polynucleotide or microarray and vice versa. A search for each of claims 39, 40, and 42 would require a different patent and non-patent literature search requiring use of different keywords and independent considerations as each of claims 39, 40, and 42 is drawn to a different method involving different method steps. Furthermore, as stated

above, claims 39, 40, and 42 are *additional* methods of use and 37 CFR § 1.475(d) does not provide for the inclusion of multiple methods of use within the main invention.

Beginning at the middle of page 12 of Paper No. 19, applicant argues claims 32-34, 39, and 40, drawn to methods of using the polynucleotide of Group XX, should be rejoined upon allowance of claims drawn to polynucleotides of Group XX. Applicant's argument is not found persuasive. It is noted that, as currently written, the methods of claims 32-34 and 40 neither make nor use the polynucleotide of Group XX and thus are not entitled to rejoinder according to MPEP § 821.04. While claim 39 is a method of using the claimed polynucleotide of Group XX, the claimed polynucleotide of Group XX is not yet allowable and rejoinder of claim 39 with the claims of Group XX is not yet required according to MPEP § 821.04. If the polynucleotide of Group XX is found to be allowable, claim 39 will then be evaluated for rejoinder according to MPEP § 821.04.

[4] The requirement is still deemed proper and is therefore made FINAL.

[5] Claims 21, 22, 32-40, and 42-45 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim.

[6] Claims drawn to an isolated polynucleotide, a recombinant polynucleotide, a cell, and a microarray (claims 23-27, 30, 31, and 41) and the first claimed method of use, i.e., a method of producing a polypeptide using a host cell comprising a recombinant polynucleotide (claims 28 and 29), are being examined on the merits.

Specification/Informalities

[7] The attempt to incorporate subject matter into this application by reference to a hyperlink embedded in the specification at for example, page 2, line 14; page 3, line 17; page 13, lines 30 and 34; and all other instances in the specification is improper. Incorporation of subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP § 608.01 regarding hyperlinks in the specification and 608.01(p), paragraph I regarding incorporation by reference.

[8] The specification is objected to as being confusing in that the specification teaches the polypeptide of SEQ ID NO:6, encoded by SEQ ID NO:22, is a hydrolase protein (see e.g., pages 1 and 20-22 of the specification), while also asserting the polypeptide of SEQ ID NO:6 is homologous to a phospholipase A2 inhibitor (see page 62 of the specification). Is the specification indicating that the polypeptide of SEQ ID NO:6 has the dual function of both a hydrolase and a hydrolase inhibitor? Based on these contradictory teachings, it is unclear as to the function of the polypeptide of SEQ ID NO:6.

Claim Objections

[9] Claims 23-29 and 41 are objected to as being dependent upon non-elected claims. It is suggested that, for example, applicant amend the claims such that they no longer depend from non-elected claims 21 and 22.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

[10] Claims 23-31 and 41 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or well-established utility. Claims 23-25, 30, and 31 are drawn to an isolated polynucleotide encoding SEQ ID NO:6 including SEQ ID NO:22 and variants and fragments thereof. Claims 26 and 27 are drawn to a recombinant polynucleotide comprising the polynucleotide of claim 23 and a cell transformed with said recombinant polynucleotide. Claims 28 and 29 are drawn to a method of producing a polypeptide of SEQ ID NO:6 and variants and fragments thereof. Claim 41 is drawn to a microarray comprising the polynucleotide of claim 23.

The claimed polynucleotide has no substantial utility as further experimentation is required to establish its "real world" use as explained in detail below. It is noted that applicant asserts the "[i]nvention relates to nucleic acid and amino acid sequences of hydrolase proteins" (page 1, line 4 of the

specification). Based on this and other disclosure in the specification (see, e.g., pages 20-22 of the specification), it would appear that applicant asserts the polypeptide of SEQ ID NO:6 encoded by SEQ ID NO:22 to have hydrolase activity. However, the specification also indicates that SEQ ID NO:6 shares an undisclosed level of sequence identity to a phospholipase A2 inhibitor isolated from the Chinese snake *Agkistrodon blomhoffi sinitcus* as disclosed by Okumura et al. (*J Biol Chem* 273:19469-19475; IDS reference 10) (page 62 of the specification). Therefore, it is unclear as to whether applicant intends for the polypeptide of SEQ ID NO:6 to have hydrolase activity or phospholipase A2 inhibitory activity. No further explanation of the activity of the polypeptide of SEQ ID NO:6 encoded by SEQ ID NO:22 is provided in the specification. As such, further experimentation would be required to determine whether the polypeptide has hydrolase activity or phospholipase A2 activity.

Based on the description of SEQ ID NO:6 in the specification at page 62, it would appear that SEQ ID NO:6 is homologous to a phospholipase A2 inhibitor based on leucine rich repeat domains. Even if applicant intends for the polypeptide of SEQ ID NO:6 to have phospholipase A2 inhibitory activity – which, as stated above, is unclear as applicant states the polypeptide has hydrolase activity and further states it is homolgous to a phospholipase A2 inhibitor - further experimentation would be required to determine whether SEQ ID NO:6 has phospholipase A2 inhibitory activity as the identity shared between SEQ ID NO:6 and the phospholipase A2 inhibitor isolated from *Agkistrodon blomhoffi sinitcus* is so low, one of ordinary skill in the art would recognize that an empirical determination of the activity of SEQ ID NO:6 is required to confirm its activity. A sequence alignment reveals there is only 24.1% identity and only 36% local similarity between SEQ ID NO:6 and *Agkistrodon blomhoffi sinitcus* phospholipase A2 (see attached sequence comparison). It appears the function of SEQ ID NO:6 has been assigned solely on the basis of a very low amino acid identity to *Agkistrodon blomhoffi sinitcus* phospholipase A2. Brenner (*Trends Genet* 15:132-133) teaches that it is impossible to determine the reliability of a functional assignment of a protein without verification by laboratory experiments (page 132, left column). Scott et al. (*Nat Genet* 21:440-443) teach an erroneous functional assignment of a protein based on 45% sequence identity and teach "[t]hese results underscore the importance of confirming the function of

newly identified gene products even when database searches reveal significant sequence homology to proteins of known function" (page 441, left column, bottom). Furthermore, the art (*Curr Opin Struc Biol* 11:725-732) teaches that leucine rich repeats are present in a number of proteins with *diverse* functions (page 725, abstract) including hormone-receptor interactions, enzyme inhibition, cell adhesion, and cellular trafficking (page 730, right column, middle). Thus, in view of the teachings of the art, the *very* low amino acid sequence identity to *Agkistrodon blomhoffi sinitcus* phospholipase A2, and the absence of an empirical functional characterization of SEQ ID NO:6, one of ordinary skill in the art would recognize that it is impossible to define the function of SEQ ID NO:6 based on the contradictory teachings of the instant specification and therefore, further experimentation would be required to determine the function of SEQ ID NO:6 in order to establish a "real world" use for the polypeptide of SEQ ID NO:6 and polynucleotide of SEQ ID NO:22. This type of utility is not considered a "substantial utility". See e.g., *Brenner v. Manson,* 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966). The specification must teach a skilled artisan how to use what is claimed and not merely provide a blueprint for further experimentation in order for an artisan to identify a use for the claimed invention. Here the claimed polynucleotide is suitable only for additional research.

Regarding a specific utility, applicant asserts various utilities for the claimed polynucleotide including use as a hybridization probe, for protein expression, as a therapeutic in the treatment of developmental disorders, proliferative disorders, and autoimmune/inflammatory disorders, and for diagnostic purposes. However, none of these asserted utilities is a specific utility for the claimed polynucleotide. The use of a polynucleotide for protein expression and hybridization is not specific as *any* polynucleotide has such utilities. Furthermore, regarding the use of the claimed polynucleotide as a therapeutic or for diagnostic purposes, it is noted that the specification fails to disclose a nexus between the claimed polynucleotide and a *specific* disease state such that the polynucleotide is useful for diagnosing or therapeutically treating a disease state or condition. Therefore, the asserted utilities are not specific to the claimed polynucleotide and are instead general utilities that would be applicable to the broad class of polynucleotides.

For the reasons stated above, the claimed polynucleotide has no specific and substantial utility.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[11] Claims 23, 26-28, 30, and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claim 23 (claims 26-28 and 41 dependent therefrom) is indefinite in the recitation of "biologically active" in part c). The specification discloses the meaning of this term as "having structural, regulatory, or biochemical functions of a naturally occurring molecule" (page 10, lines 13-14 of the specification). However, the scope of activities encompassed by this term is vague and it is unclear from the definition of this term what functions of the encoded polypeptide of SEQ ID NO:6 applicant intends as the meaning of "biologically active". It is suggested that the term "biologically active" be replaced with a term that clearly defines applicant's intended biological function.

[b] Claim 30 is indefinite in the recitation of "complementary" in parts c) and d). The specification defines the term "complementary" as "'partial' such that only some of the nucleotides bind" or "'complete' such that total complementarity exists between the single stranded molecules" (page 10, lines 20-21 of the specification). As such, it is unclear as to whether the complementary polynucleotides are partial or complete complements. In the interest of advancing prosecution, the term "complementary" has been interpreted as completely complementary. If the examiner's interpretation of the term is incorrect, applicant should so state and clarify the record. It is suggested that applicant clarify the meaning of the term "complementary" as being either a partial or complete complement.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[12] Claims 23, 26-28, 30, 31, and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of he claimed invention.

Claim 23 (claims 26, 27, and 41 dependent therefrom) is drawn (in relevant part) to a genus of isolated polynucleotides encoding a polypeptide comprising a naturally occurring amino acid sequence that is at least 90% identical to SEQ ID NO:6 and biologically active fragments of a polypeptide having SEQ ID NO:6. Claim 28 is drawn (in relevant part) to a method for producing a genus of polypeptides using a cell comprising a genus of recombinant polynucleotides encoding a polypeptide comprising a naturally occurring amino acid sequence that is at least 90% identical to SEQ ID NO:6 and biologically active fragments of a polypeptide having SEQ ID NO:6. Claim 30 is drawn (in relevant part) to an isolated polynucleotide comprising a naturally occurring sequence at least 90% identical to SEQ ID NO:22, a complement thereof, and RNA equivalents thereof. Claim 31 is drawn to an isolated polynucleotide comprising at least 30 contiguous nucleotides of SEQ ID NO:22.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a *representative number of species* by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only a single representative species of the genus of claimed polynucleotides, i.e., the polynucleotide of SEQ ID NO:22. The specification fails to describe any additional representative species of the claimed genus. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it is also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". In the instant case, the claimed genus of polynucleotides encompasses species that are widely variant in both structure and function, including (but not limited to) genomic sequences, allelic variants, and nucleic acid variants encoding polypeptides having function other than the activity of SEQ ID NO:6, e.g., non-functional polypeptides and polypeptides having enzymatic activity other than the asserted hydrolase activity. As such, the disclosure of the single representative species of SEQ ID NO:22 is insufficient to be representative of the attributes and features of *all* species encompassed by the claimed genus of polynucleotides. Given the lack of description of a representative number of polynucleotides, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[13] Claims 23-31 and 41 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial or specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

[14] Even if applicant demonstrates the polynucleotide encoding SEQ ID NO:22 has a specific and substantial or well-established utility, the following rejection still applies. Claims 23, 26-28, 30, 31, and 41 are rejected under 35 U.S.C. 112, first paragraph, because the specification is not enabling for the broad scope of claimed polynucleotides and polypeptides produced using said polynucleotide. Regarding claims

23 (claims 26, 27, and 41 dependent therefrom), 30, and 31, the specification, while being enabling for a polynucleotide encoding SEQ ID NO:6 including SEQ ID NO:22, does not reasonably provide enablement for the broad scope of claimed polynucleotides, including *all* polynucleotides encoding polypeptides comprising a naturally occurring amino acid sequence that is at least 90% identical to SEQ ID NO:6, *all* polynucleotides encoding biologically active fragments of a polypeptide having SEQ ID NO:6, *all* polynucleotides comprising a naturally occurring sequence at least 90% identical to SEQ ID NO:22 and complements and RNA equivalents thereof (claim 30), and *all* polynucleotides comprising at least 30 contiguous nucleotides of SEQ ID NO:22 (claim 31). Regarding claim 28, the specification, while being enabling for a method of producing the polypeptide of SEQ ID NO:6 using a host cell transformed with a polynucleotide encoding SEQ ID NO:6, does not reasonably provide enablement for a method for producing the broad scope of polypeptides of claim 21. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

- The claims are overly broad in scope: The claims are so broad as to encompass *all* polynucleotides encoding polypeptides comprising a naturally occurring amino acid sequence that is at least 90% identical to SEQ ID NO:6, *all* polynucleotides encoding biologically active fragments of a

polypeptide having SEQ ID NO:6, *all* polynucleotides comprising a naturally occurring sequence at least 90% identical to SEQ ID NO:22 and complements and RNA equivalents thereof, *all* polynucleotides comprising at least 30 contiguous nucleotides of SEQ ID NO:22, and a method for producing *all* polypeptides of claim 21 using *all* recombinant polynucleotides encoding therefor. The broad scope of claimed polynucleotides or polynucleotides recited in the method of claim 28 are not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides broadly encompassed by the claims. In this case the disclosure is limited to a polynucleotide encoding SEQ ID NO:6 including SEQ ID NO:22 and a method of producing the polypeptide of SEQ ID NO:6 using a host cell transformed with a polynucleotide encoding SEQ ID NO:6.

- The lack of guidance and working examples: The specification provides only a single working example of the claimed polynucleotide, i.e., SEQ ID NO:22 and only a single working example of a polypeptide produced using a host cell transformed with a recombinant polynucleotide, i.e., SEQ ID NO:6. These working examples fail to provide the necessary guidance for making and/or using the entire scope of polynucleotides. The specification fails to provide guidance regarding those nucleotides of SEQ ID NO:22 or amino acids of SEQ ID NO:6 that may be altered by substitution, addition, insertion, and/or deletion with an expectation of maintaining the desired activity. Furthermore, the specification fails to provide guidance as to how to use those variant nucleic acids – both naturally and non-naturally occurring - that encode polypeptides having activities other than the desired activity, e.g., nucleic acids encoding non-functional polypeptides or polypeptides having activity other than SEQ ID NO:6.

- The high degree of unpredictability in the art: The nucleotide sequence of an encoding nucleic acid determines the corresponding encoded protein's structural and functional properties. Predictability of which changes can be tolerated in an encoded protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function.

The positions within an encoding nucleic acid's sequence where modifications can be made with a reasonable expectation of success in obtaining an encoded polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. In this case, the necessary guidance has not been provided in the specification as explained in detail above. Thus, a skilled artisan would recognize the high degree of unpredictability that the entire scope of polynucleotides would encode a polypeptide having the desired activity. The ability to assign a protein's function based on similarities to other proteins, even those that are naturally occurring, is *highly* unpredictable.

- The state of the prior art supports the high degree of unpredictability: The state of the art provides evidence for the high degree of unpredictability in altering a polynucleotide sequence with an expectation that the encoded polypeptide will maintain the desired activity/utility. For example, Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York, 1991) teach "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability... ...they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247). While it is acknowledged that this reference was published in 1991, to date there remains no certain method for reasonably predicting the effects of even a *single* amino acid mutation on a protein. Such mutations may even completely alter a protein's activity. As a representative example, Witkowski et al. (*Biochemistry* 38:11643-11650) teaches that a single amino acid substitution results in conversion of the parent polypeptide's activity from a beta-ketoacyl synthase to a malonyl decarboxylase (see e.g., Table 1, page 11647). Thus, the prior art acknowledges the unpredictability of altering a protein-encoding sequence with an expectation of obtaining a protein having a desired function and discloses that even a single substitution in a polypeptide's amino acid sequence may completely alter the function of a

polypeptide. The state of the art also provides evidence for the high degree of unpredictability that sequence identity shared between two polypeptide sequences can be used to assign function to a polypeptide. For example, Brenner (*Trends Genet* 15:132-133) teaches that it is impossible to determine the reliability of a functional assignment of a protein without verification by laboratory experiments (page 132, left column). Further evidence is provided by Scott et al. (*Nat Genet* 21:440-443) who teach an erroneous functional assignment of a protein based on 45% sequence identity between the proteins. Scott et al. teach "[t]hese results underscore the importance of confirming the function of newly identified gene products even when database searches reveal significant sequence homology to proteins of known function (page 441, left column, bottom).

- The amount of experimentation required is undue: While methods of generating variants of a given polynucleotide, e.g., mutagenesis, and methods of isolating homologous polynucleotides, e.g., hybridization, are known, it is not routine in the art to screen for *all* polynucleotides having a substantial number of substitutions or modifications and encoding polypeptides having *any* function, as encompassed by the instant claims. Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high degree of unpredictability as evidenced by the prior art, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

[15] Applicant's claim for domestic priority under 35 USC § 119(e) to provisional applications 60/172,256, filed November 12, 1998, and 60/135,519, filed May 21, 1999, is acknowledged. The sequences of SEQ ID NO:6 and 22 of the instant application are disclosed in provisional application number 60/135,519 as SEQ ID NO:5 and 20, respectively. Applicant is granted the benefit of the earlier filing date of provisional application 60/135,519 to the extent this provisional application provides support for the claimed subject matter. Accordingly, the following rejection(s) have been made based on a priority date of May 21, 1999.

[16] Claims 23, 26-28, 31, and 41 are rejected under 35 U.S.C. 102(a) as being anticipated by Jacobs et al. (WO 98/45437). Claim 23 is drawn (in relevant part) to an isolated polynucleotide encoding a biologically active fragment of SEQ ID NO:6. Claim 26 is drawn to a recombinant polynucleotide comprising a promoter linked to the polynucleotide of claim 23. Claim 27 is drawn to a cell transformed with the polynucleotide of claim 26. Claim 28 is drawn to a method of producing a polypeptide of claim 21 using a cell transformed with a recombinant polynucleotide comprising a polynucleotide encoding the polypeptide of claim 21. Claim 31 is drawn to an isolated polynucleotide comprising at least 30 contiguous nucleotides of SEQ ID NO:22. Claim 41 is drawn to a microarray comprising the polynucleotide of claim 23. Jacobs et al. teach a nucleic acid that is 100% identical to nucleotides 69-469 and 471-722 of SEQ ID NO:22 and encodes a polypeptide that is 100% identical to amino acids 1-132 of SEQ ID NO:6 (see attached sequence alignments). Jacobs et al. teach their polynucleotide may be operatively linked to an expression control sequence (page 59, lines 28-32) and used to transform a host

cell (page 60, lines 2-3) and teach a method for producing the expressed polypeptide by culturing the host cell and purifying the resulting expressed protein (page 60, lines 28-32). Jacobs et al. teach their nucleic acid can be attached to a gene chip (page 63, lines 27-28). This anticipates claims 23, 26-28, 31, and 41 as written.

[17] Claim 31 is rejected under 35 U.S.C. 102(b) as being anticipated by Database GenBank Accession Number AA622495. Claim 31 is drawn to an isolated polynucleotide comprising at least 30 contiguous nucleotides of SEQ ID NO:22. Database GenBank Accession Number AA622495 teaches a nucleic acid that is 100% identical to nucleotides 1471-1834 of SEQ ID NO:22 (see attached sequence alignment). This anticipates claim 31 as written.

Conclusion

[18] Status of the claims:

- Claims 21-45 are pending.
- Claims 21, 22, 32-40, and 42-45 are withdrawn from consideration.
- Claims 23-31 and 41 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:00 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for submission of official papers to Group 1600 is (703) 308-4242. Draft or informal FAX communications should be directed to (703) 746-5078. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

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